accuracy (89% vs 84%), and negative predictive accuracy (94% vs 78%). The enhanced results are probably due to the improved signal-to-noise ratio with the higher-field strength. It therefore seems likely that 3-T may become the preferred cardiac MR field strength of choice for performance of myocardial perfusion assessments. ■

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Acute Coronary Syndrome

Cardiovascular Events After Clopidogrel Discontinuation

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Incidence of Death and Acute Myocardial Infarction Associated With Stopping Clopidogrel After Acute Coronary Syndrome

Ho PM, Peterson ED, Wang L, et al.

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Clopidogrel is currently recommended for all patients following an acute coronary syndrome (ACS) event. Although patients treated medically or with a bare-metal stent should remain on clopidogrel for at least 1 month (and ideally up to 1 year), those with a drug-eluting stent are recommended to be maintained on the drug for at least 1 year.[1] Previously, a "rebound effect" has been demonstrated with some cardiovascular drugs, like aspirin, heparin, and beta-blockers, with patients experiencing a clustering of acute events following abrupt cessation of drug therapy.[2-4] A recent study has demonstrated an increase in platelet and inflammatory biomarkers after discontinuation of thienopyridine therapy in diabetic patients with coronary artery disease.[5] As a result, concerns have been expressed about a possible rebound effect from clopidogrel.[6]

To explore whether a "clopidogrel rebound" exists for clinical events, Ho and colleagues[7] retrospectively evaluated the frequency and timing of adverse events (a composite of all-cause mortality or acute myocardial infarction [AMI]) following cessation of clopidogrel therapy for ACS. The study cohort consisted of 3137 ACS patients from 127 Veterans Affairs hospitals who had been discharged on clopidogrel therapy. Duration of clopidogrel usage was indirectly derived using prescription refill data from pharmacy dispensing records, introducing a probable source of bias. Results were analyzed separately for patient groups managed medically or with percutaneous coronary intervention (PCI).

In the 1568 patients in the medical management group, mean duration of clopidogrel was 302 (± 151) days. Follow-up information for these patients was gathered at a mean of 196 (± 152) days after clopidogrel treatment was stopped. Prevalence of comorbid conditions was higher in this group. Death (n = 155) or AMI (n = 113) occurred in 17.1% of these patients. A preponderance of adverse events (60.8%) occurred during the initial 90-day interval after clopidogrel was discontinued. Only 9.7% of the adverse events occurred during 181 to 270 days of follow-up. Even after adjustment for duration of clopidogrel therapy as part of a multivariable analysis, the initial 90-day period was associated with an approximate 2-fold risk of death or AMI compared with the next 91 to 180 days (incidence rate ratio [IRR], 1.98; 95% confidence interval [CI], 1.46-2.69).

Similar findings were demonstrated in 1569 PCI-treated ACS patients. Mean duration of clopidogrel treatment was 278 (± 169) days, and patients were monitored for 203 (± 148) days after stopping the drug. All-cause mortality (n = 68) or AMI (n = 56) occurred in 7.9% of the patients. A majority of events (58.9%) occurred between 0 and 90 days after clopidogrel was discontinued. As in the medically managed group, the risk for adverse events (IRR, 1.82; 95% CI, 1.17-2.83) was approximately double during the first 90 days after discontinuation of the drug, even after adjustment for multiple covariates.

Observations

This study raises interesting issues. First, it suggests a possible rebound effect, potentially due to increases in platelet reactivity. It should be noted, though, that no apparent increase in event rates was seen in the Clopidogrel for the Reduction of Events During Observation (CREDO) randomized trial of clopidogrel in elective PCI.[8] Examination of other databases and trials is required to try to confirm these data. Second, it suggests that the issue of recurrent events after stopping clopidogrel prior to the recommended 1-year treatment period exists not just in patients who receive stents but also in those who receive medical treatment.

Another issue to consider when looking at this study is that the mean duration of therapy in both groups was 9 to 10 months, slightly less than the currently recommended ideal period of 1 year. The wide standard deviations in duration of therapy indicate that a substantial number of patients did not receive clopidogrel for the recommended duration. However, the increased risk during the first 0 to 90 days after discontinuation of therapy was seen consistently among patients taking clopidogrel for 3 or 6 months, 9 months, or more than 9 months after ACS hospital discharge, suggesting that this risk may persist even if a 1-year duration of clopidogrel is followed. In addition, when rates of AMI alone, instead of the composite outcome, were evaluated for the first 30 days, a similar rebound effect was seen.

The study cohort was almost exclusively (98%) male. Therefore, it is not clear whether these findings can be extrapolated to women with ACS. Besides the inherent bias in the retrospective observational design, the study specifically excluded patients who had an adverse event while on clopidogrel, thus lowering the overall risk profile of the subjects. The authors did not provide specific reasons for the discontinuation of clopidogrel—whether patients simply ran out of medication or whether they were stopped by the provider prematurely due to poor clinical condition or drug-related complications—which could have selective influence on adverse event rates in the initial 30-day period.

Currently, more than 80% of the PCI procedures performed in the United States involve drug-eluting stents (DES),[9] although that percentage has shifted recently due to the concerns of late stent thrombosis in DES-treated patients. In this study, only 37.3% of the PCI-treated subjects received a DES, making the results less applicable to current ACS patients receiving coronary stents. Due to the limited numbers, a subgroup analysis for IRR was not performed in these patients. Recent data suggest that DES may be associated with an increased rate of late stent thrombosis and adverse events, particularly in patients not receiving clopidogrel.[10,11] Thus, this study may have had a lower adverse event rate after clopidogrel withdrawal than might be seen in current practice due to the lower proportion of DES-treated patients in the cohort. Although several studies have implicated a stent-related etiology for the increase in adverse cardiac events after discontinuation of thienopyridine therapy,[12] the results from the medically managed group treated without a stent suggest that at least part of the recurrent events might be attributable to a potential clopidogrel rebound. It is not clear, though, if it is truly rebound—as suggested in this observational study—or a lack of protection once clopidogrel is withdrawn. Further studies, ideally from randomized cohorts where stopping clopidogrel is planned, will help clarify these issues.

Recommendations

Ho and colleagues[7] offer some speculation on how to avoid the apparent increase in events after clopidogrel is discontinued. One potential idea is to simply extend the duration of clopidogrel, although one would need to consider the potential for increased risk of bleeding complications (as well as the increased cost). The authors suggest that possible alternative approaches could include a gradual tapering of the drug, use of increased doses of aspirin or heparin as bridging therapy, or substitution of ticlopidine during the final weeks of clopidogrel therapy, although none of these approaches have been tested.

It is essential to emphasize that clopidogrel is of proven benefit in post-ACS patients,[1] and the absolute adverse event rates within 90 days of drug discontinuation were low, especially in those treated with PCI (1.31 [95% CI, 1.12-1.53] per 1000 patient-days for medically managed groups and 0.57 [95% CI, 0.45-0.72] per 1000 patient-days for PCI groups). The current study by itself does not merit revision of guidelines related to clopidogrel therapy in ACS patients. However, it does reinforce the need to ensure compliance with antiplatelet therapy for the recommended duration of 1 year. The recent guidelines from the American College of Cardiology/American Heart Association/Society for Cardiovascular Angiography and Interventions note that all high-risk patients should be closely monitored, and during the first year, clopidogrel should not be stopped for dental, gastrointestinal, or other minor procedures, unless absolutely necessary.[13] At the end of that time, an analysis of the risks and benefits of continuing the drug is warranted, with consideration of individual patient characteristics. Patients who do not have any bleeding complications while on clopidogrel might continue therapy beyond 1 year.

A prospective, randomized, controlled trial is the logical next step to conclusively demonstrate the existence of a "clopidogrel rebound." Observational studies from other databases of ACS patients will also be helpful in this regard. The magnitude of adverse events needs to be further explored to elucidate whether this is a true rebound effect as opposed to a mere loss of benefit. Finally, further research is needed to examine the mechanisms of this potential phenomenon, so that adequate preventive strategies can be developed. ■

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